

Malaria

**COL Arthur Lyons, PhD, MD, FACP, FIDSA
Deputy Commander for Clinical Services
DiLorenzo TRICARE Health Clinic, Pentagon
Washington, DC**

Disclosures

- **Conflict of interest:**
 - I have no patents or financial interest in the antigens and vaccines discussed today
- **Pre-clinical:**
 - All pre-clinical work was conducted under IACUC approved protocols in AAALAC-accredited facilities
- **Clinical & Field Trials:**
 - Informed consent was obtained prior to screening and enrolment
 - Trials were conducted according to ICH and FDA guidelines
- **Non-official:**
 - All opinions expressed are personal and are not official

Overview

- Malaria is a large global problem
- Current strategies are inadequate
- DoD is making progress towards malaria solutions
- Multi-pronged efforts are ongoing



What is Malaria?

- Potentially lethal parasitic disease (*Plasmodium* species)
- Transmitted between humans (reservoir) by mosquitoes (the vector)

- **Initial malaria** → fever, chills, muscle aches, headaches, fatigue, rigors

ACUTE ILLNESS

- **Untreated** →  severe anemia, kidney failure, coma, convulsions

DEATH

- **Survivors** → Often become chronic carriers

ILL HEALTH, LEARNING DISABLED

RESERVOIRS OF INFECTION

UNCLASSIFIED//FOUO

History

- Chinese writings (2700 BC)
- The Eber's papyrus (1550 BC)
- Hippocrates (described malaria fevers)
- Greek civilizations affected by “bad air”, the rich summered in the highlands
- Malaria in the United States???
 - First military expenditure in 1775 (\$300) for quinine to protect G. Washington's troops
 - In Civil War (1861-65) 50% white and 80% of black troops w/ malaria annually

The Situation is Dire

- Malaria is a personal tragedy
 - Death in infants and in 1st pregnancies
 - Sickness, long term disability, chronic illness in survivors
- Malaria is a global health tragedy
 - Malaria kills 3,000 children a day
 - Malaria hastens spread of HIV infection**
- Malaria is an economic-political tragedy
 - Major cause of disability adjusted life years (DALYS)
 - Prevents development, especially in Africa
 - A cause and a consequence of poverty

**Abu-Raddad L et al. Links: Dual infection with HIV and malaria fuels the spread of both diseases in sub-Saharan Africa. Science 2006;314:1605-6



The Global Malaria Problem

- **#1 cause of death of young African child**
- **Malaria is resurgent:**
 - **More cases now than ever in history**
- **Inadequate prevention:**
 - **Bed nets save lives - but not widely used**
 - **DDT/insecticides save lives - but not widely used**
- **Inadequate treatment**
 - **Poor diagnosis -**
 - **Drug resistance:**
 - **affordable drugs not effective**
 - **effective drugs not affordable**
- **No malaria vaccine yet licensed**



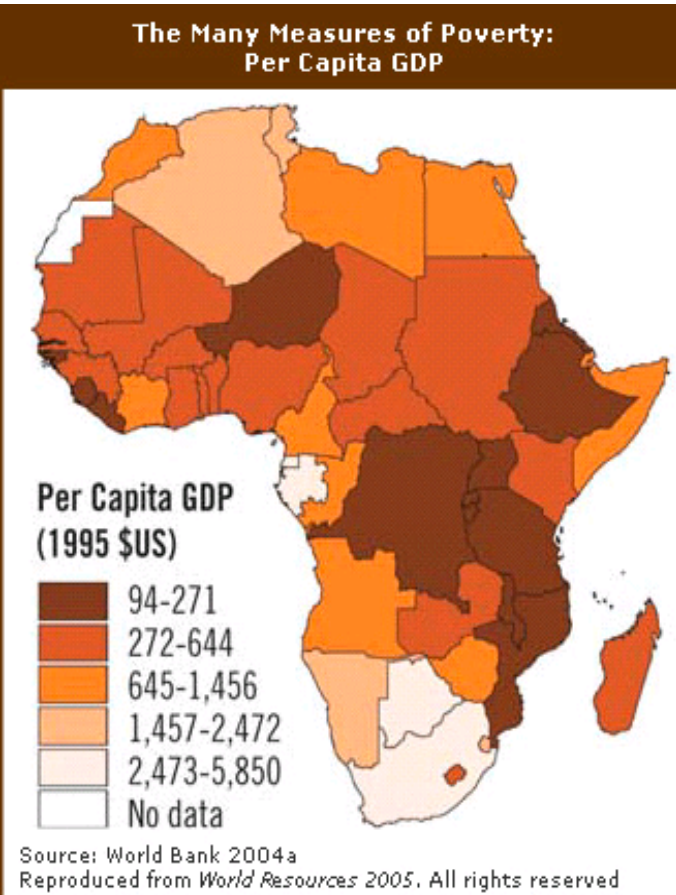
Hand of child with severe malaria anemia in the palm of his mother



Child with severe malaria

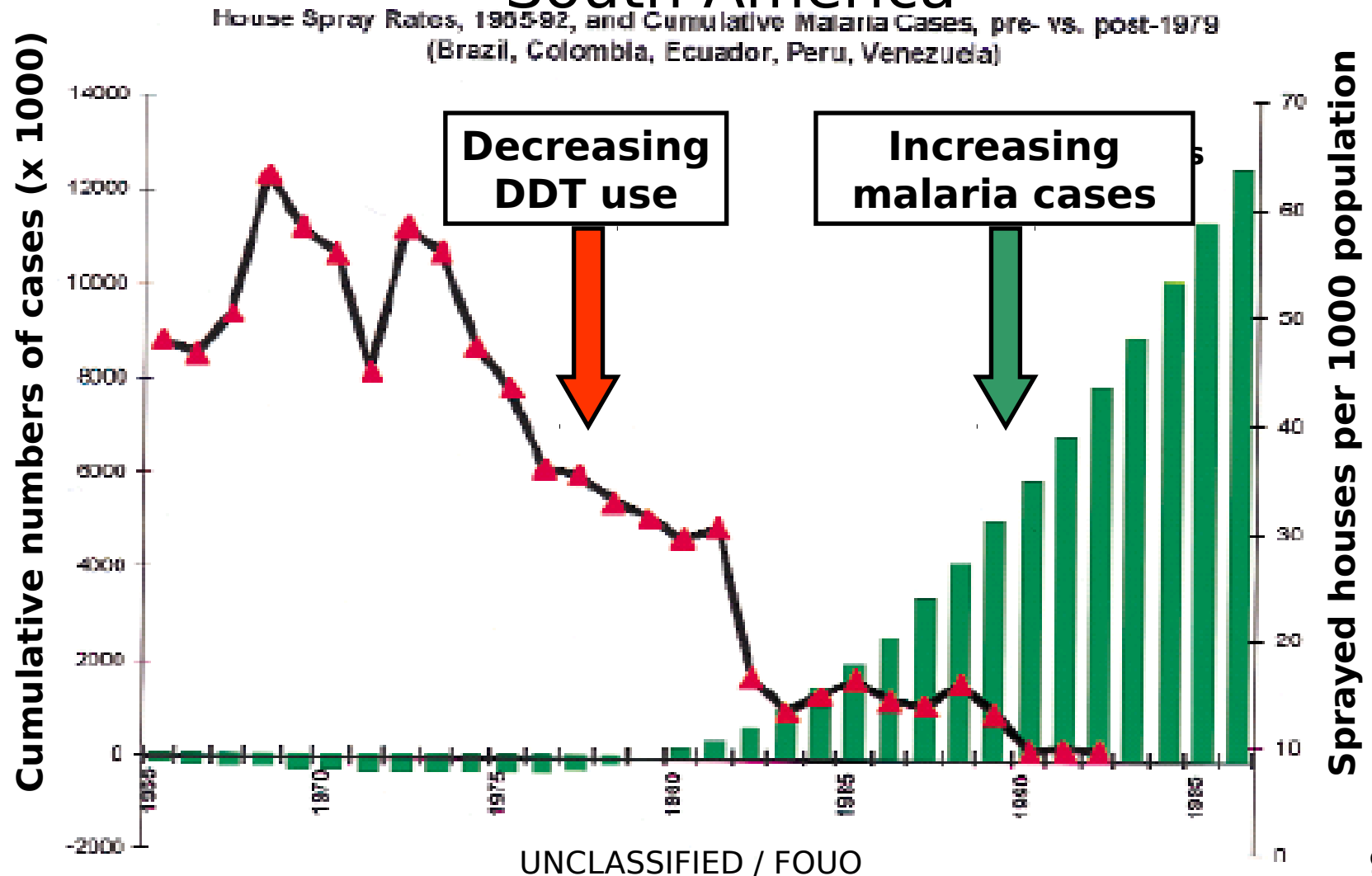
UNCLASSIFIED / FOUO

ITNs - Insecticide Treated Nets



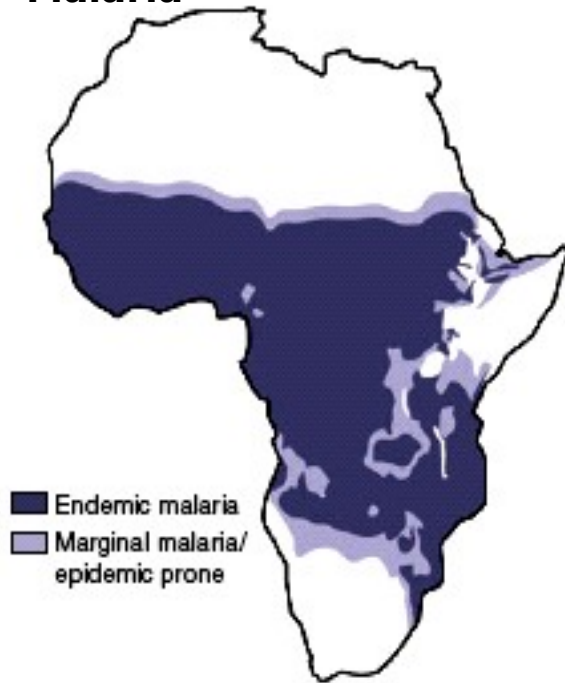
- ITNs versus no nets // protective effect
 - 50% reduction in malaria attacks
 - 45% reduction in severe malaria attack
 - 17% reduction in death
- Additional benefits
 - Improved maternal health & hematocrits
 - Improved infant health & birth weights
- Cost: about \$6
- Cost effective: Yes
- Usage: Less than 10% of children at risk
- Issues:
 - Too expensive for poor users to purchase
 - Requires retreatment with insecticide
 - Requires repair
 - Requires education to promote use

Indoor Residual Spraying (IRS) DDT Use and Cumulative Malaria Cases in South America



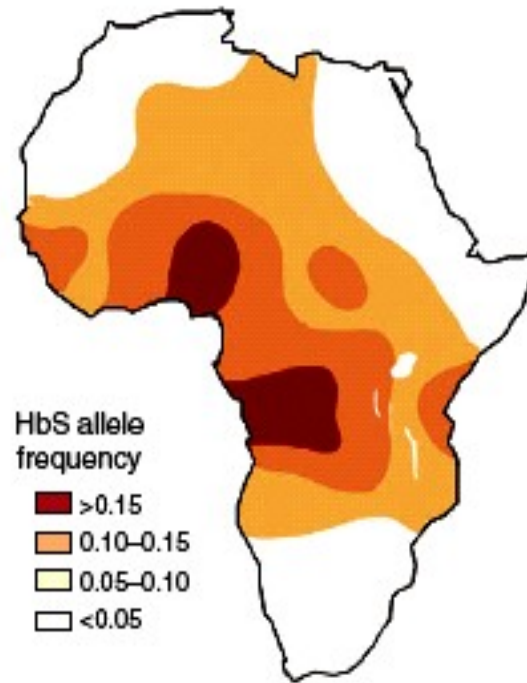
Distribution of Malaria & Abnormal Hemoglobin Genes in Africa

Malaria



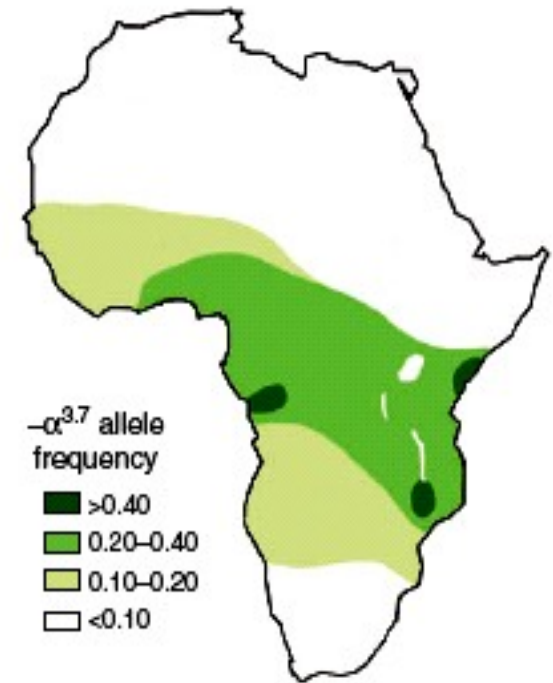
Historic distribution of malaria in Africa

Sickle-cell



Protection against severe and lethal malaria

Alpha-thalassaemia

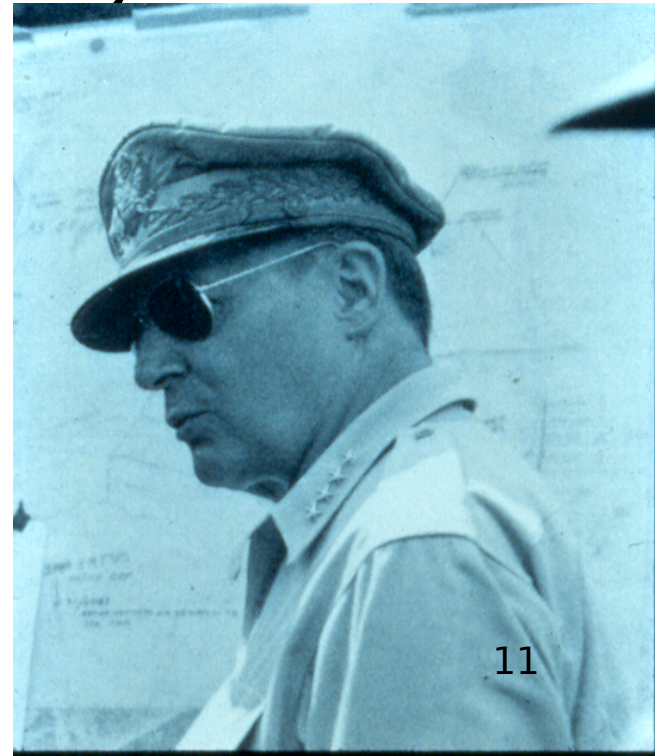


Protection against severe malaria anemia

- Haldane's hypothesis explains human abnormal red cell enzymes (G6PD), hemoglobins (Hb C, Hb E, Hb S) and red cell surface proteins (loss of Duffy antigen) as balanced polymorphisms in the context of malaria

- *"Doctor, this will be a long war if for every division I have facing the enemy, I must count on a second division in hospital with malaria and a third division convalescing from this debilitating disease".*

General Douglas MacArthur, May 1943 to Colonel Paul F. Russell, MC, the American army malaria consultant.



Destabilization Effect

- There are huge impacts of HIV/AIDS, malaria, and MTb on the critical infrastructures that sustain the security, stability, and viability of modern nation-states
- In the developing world (esp Africa) these diseases undermine education and health systems, economic growth, micro enterprises, policing and military capabilities, political legitimacy, family structures, and overall social cohesion
- Undermine the stability of already weakened states, adds to their vulnerability to extremists/terrorists who will seek to corrupt or coerce them into providing converts, cover, or cooperation
- The real global war can be thought of being against these diseases - needs to be comprehensive, fought at many levels and on many fronts

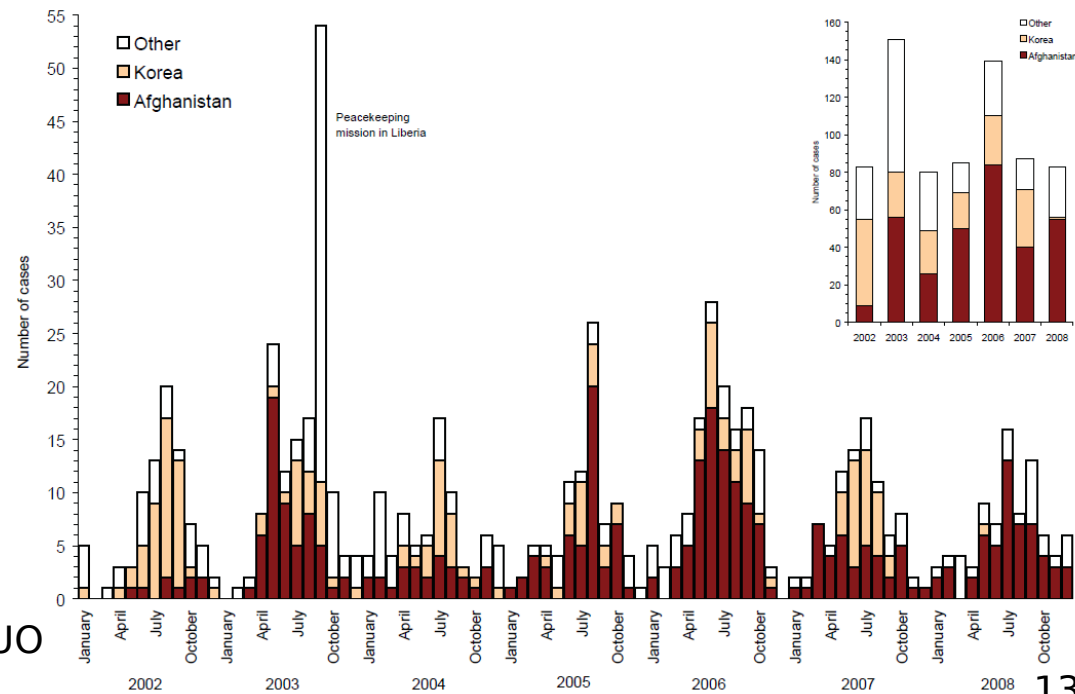
Recent Military History

- US / Somalia 1992-3 (233 cases; 77% *P. vivax*)
- US Army 1995-2002
 - 30-75 cases/yr;
 - ~ 75% *P. vivax*
- US/ Afghanistan 2002 (38 cases)
- US / Liberia 2003 (80 cases)
- US/ Afghanistan today (>100 cases/yr)
- US/ Haiti 2010 (10 cases)
- Liberia 2009 (multiple cases, 1 death)
- Liberia 2010 (7 cases)

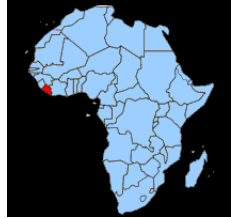
UNCLASSIFIED / FOUO



Figure 2. Malaria cases among U.S. service members, by estimated location of infection acquisition and month and year (inset) of clinical diagnosis/report, U.S. Armed Forces, January 2002-December 2008



Joint Task Force Liberia 2003



- 225 Marines in Monrovia, Liberia < 2 weeks
 - Attack rate = 36% (80/225)
 - Evacuated to USA = 19% (43/225)
 - Severe = 2% (5/225)
 - 5 in intensive care unit
 - 4 on ventilators
- Prevention for military (travelers)
 - Difficult in operational areas
 - Requires consistent, reliable use of:
 - Mosquito repellants
 - Bed nets
 - Treated uniforms
 - Antimalarial drugs (drug-resistance, side-effect & compliance)
- Diagnostic / treatment delay = high risk severe disease
- Vaccine would be of great benefit



ANASTASIS

CORTICIS PERUVIÆ,

SEU

CHINÆ CHINÆ

DEFENSIO,

SEBASTIANI BADI GENVENSIS

Præcipue utilis Nephriticis et in Malaria,

Et

Publicæ Sanitatis in Chocoma Confabrocin.

Comit

VENTILATIONES

IOANNIS IACOBI CHIFLETII,

Remittique

VOPICI FORTVNATI FLEMPEL,

Belgicus Medicorum.

*Opus in omni libro diffinitum, et in his Decembris
Atelinet, et Philofophia.*

ILLVSTRISSIMO D.

IOANNI LVCA DVRATIO



GENEVE, Typis Franc. Moret' d'Arce. M. DC. LXXV.
Impressum in Italia.

- Jesuit's Bark, due to alkaloids, is the most celebrated specific remedy for all forms of malaria. It is obtained from several species of the genus cinchona, of the order Rubiaceae
- 1630: Countess Chinchon, the wife of Spanish Viceroy, was saved from terminal malaria by bark powders recommended by the Jesuits of Saint Paul's College in Lima, Peru
- 1632: Jesuit Barnabe' de Cobo (1582-1657) rendered important services in the exploration of Mexico and Peru. In his capacity of procurator of the Peruvian province of his order, he brought the bark from Lima to

Plasmodium falciparum Becomes Resistant to Antimalarial Drugs

Continuous New Drug Development and Licensure is Required

Drug	Introduced	First Reported Resistance	Difference (Years)
Quinine	1632	1910	278
**Chloroquine	1945	1957	12
**Proguanil	1948	1949	1
**Sulfadoxine-pyrimethamine	1967	1967	0
**Mefloquine	1977	1982	5
***Malarone	1997	2002	5

***Malarone for US FDA approval

UNCLASSIFIED / FOUO



Quinine



Chloroquine



Proguanil



Fansidar

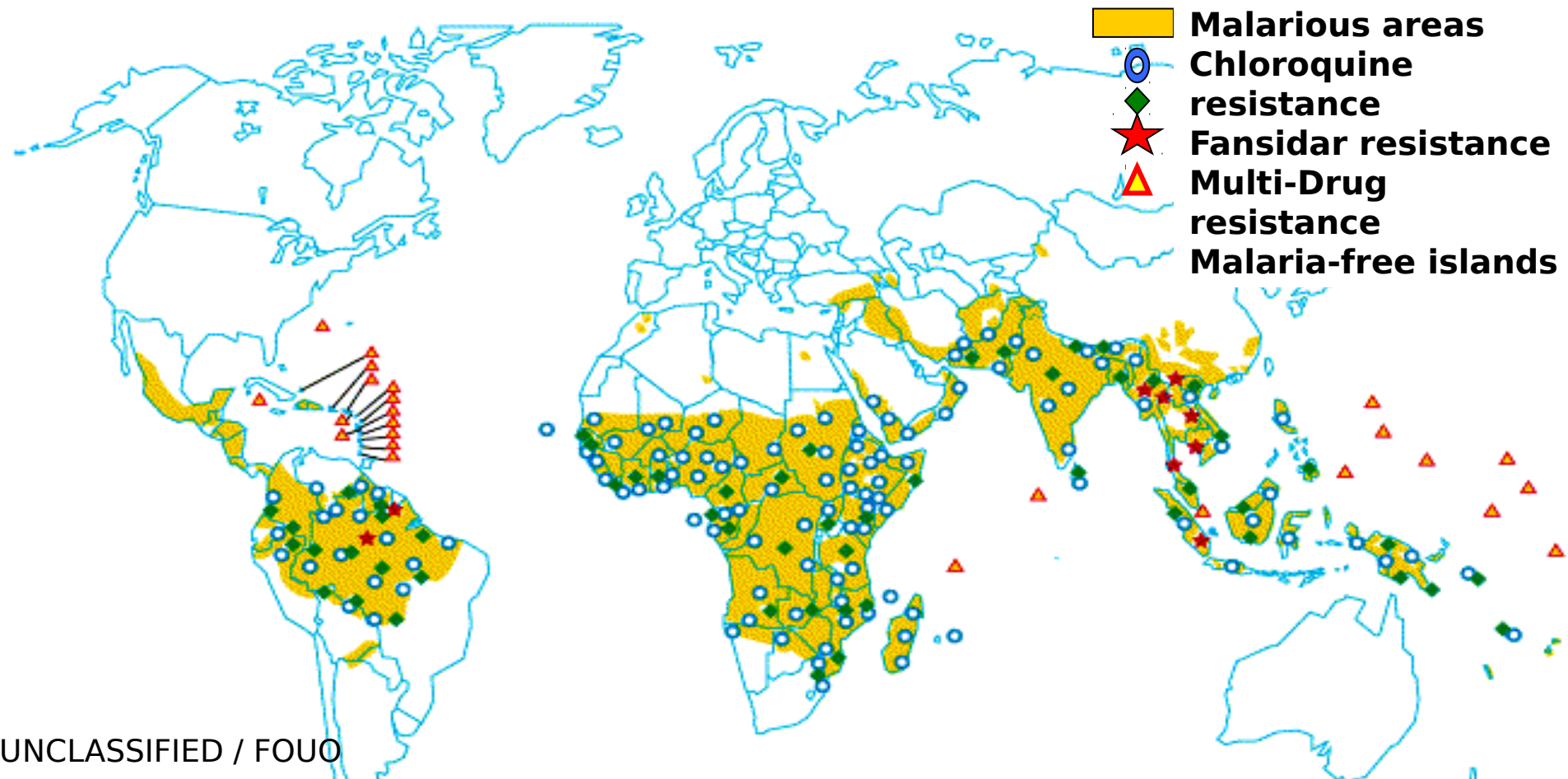


Mefloquine



Malarone

Multi-Drug Resistant *Falciparum* Malaria Means that Effective Drugs (ACTs) are not Affordable



UNCLASSIFIED / FOUO

In 1900; 53% land area malarious; 890,000,000 people at risk
In 2002; 27% land area malarious; 3,400,000,000 people at risk

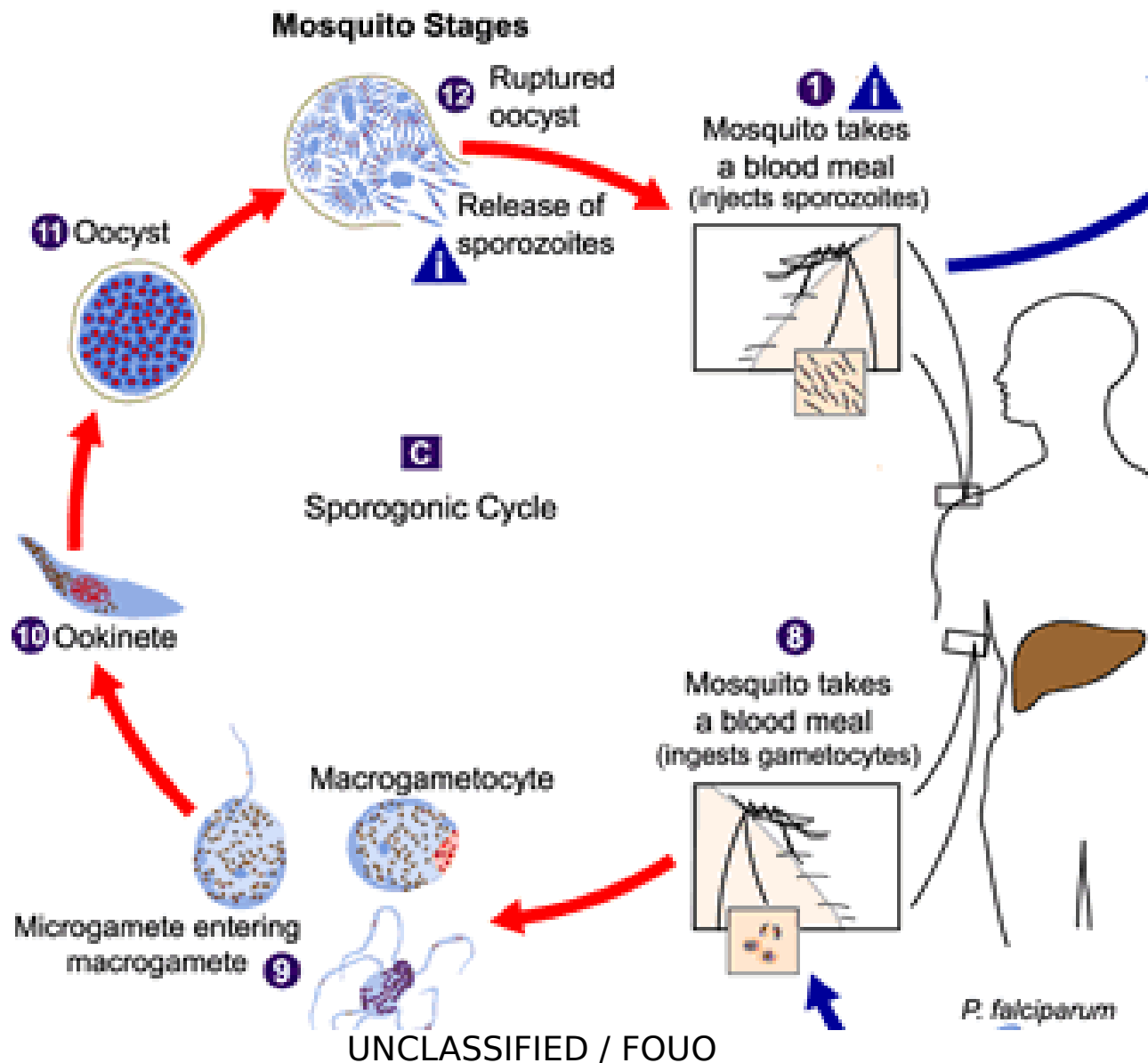
17

P. vivax: chloroquine prophylactic
or treatment failure

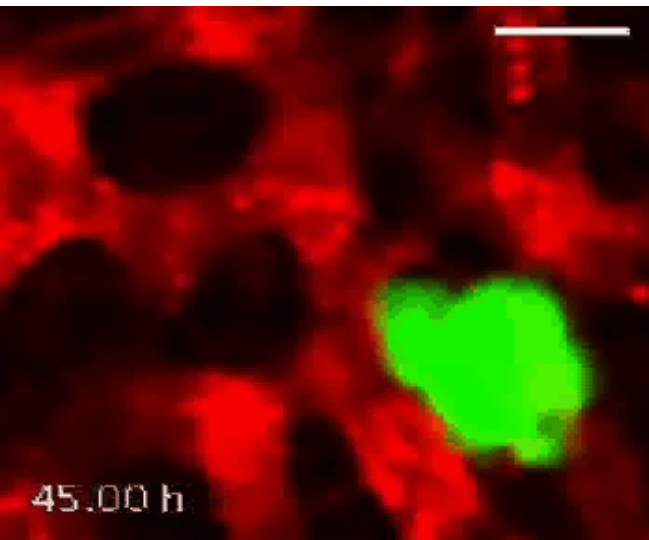


UNCLASSIFIED / FOUO

Malaria Development in Mosquitoes



From Red Cell to Red Cell and Again



**RED = LIVER CELLS
GREEN = MALARIA
PARASITES**

ACTION

- LIVER CELL BURSTS
- PARASITES ESCAPE



**RED = NORMAL RBC
BLUE = MALARIA
PARASITE
BLACK = INFECTED RBC**

ACTION

- INVADES RBC
- RBC SWELLS
- RBC RIGID
- RBC STICKY KNOBS



**RED = NORMAL RBC
BLUE = MALARIA
PARASITE
BLACK = INFECTED RBC**

ACTION

- INFECTED RBC STICKS TO BLOOD

Anopheline Mosquitos



- 50->80 species capable of transmission
- <40 really important
- Female requires blood meals for egg broods

UNCLASSIFIED / FOUO

Anopheline Mosquitos

- Life cycle – 7 to 20 days (egg to adult)
 - egg -> larva -> pupa -> adult
 - Females mate once and lay 200-1000 eggs in 3-12 batches over a lifetime
 - Find their host by chemical and physical stimuli
 - Average life span of mosquito < 3 weeks
- Malaria development – 7 to 12 days
 - Each male & female gametocyte produce >10,000 sporozoites

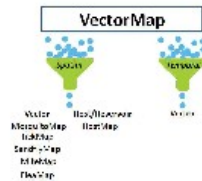


VectorMap

Know the vector, know the threat



[Home](#) | [About](#) | [Contact us](#) | [WRBU](#) | [MosquitoMap](#) | [SandflyMap](#) | [TickMap](#) | [Resources](#)



Welcome to VectorMap !

VectorMap is a product of the Walter Reed Biosystematics Unit limited in the Smithsonian Institution. VectorMap provides disease maps, and mapped collection data and distribution models for arthropod disease vector species, including mosquitoes, ticks, sand flies, mites, and fleas, as well as the hosts/reservoirs of vector-borne disease pathogens. Collection records are searchable and downloadable, users can map and contribute their own georeferenced collection data or distribution models, and all contributions have full attribution. Currently, MosquitoMap has 314,443 records, TickMap has 56,158 records, and SandflyMap has 7,930 records. In addition, there are 8,209 flea records, as well as a small number of chigger mite, mite-borne scrub typhus, and host/reservoir records.

[WHAT'S NEW?](#)>>>>>>>>>>[Take the VECTORMAP SURVEY!](#)>>>>>>>>>>[VECTORMAP TUTORIAL](#)

VectorMap is designed to preserve and make available the results of past collecting and distribution modeling activity, and to provide a unique resource for exploring possible disease risk factors. The utility of VectorMap will increase as more records and models are added. Contributions are encouraged, especially from individuals and organizations with digitized, georeferenced records and those involved in ongoing mosquito surveillance. VectorMap is modeled on MosquitoMap - see [International Journal of Health](#)

Geographics. For an introduction to georeferencing standards and procedures see *Journal of Medical Entomology*.

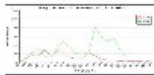
MosquitoMap is useful for:

Informing decisions about where mosquito collection efforts should be directed
Identifying areas relevant to the study of mosquito biogeography, evolution and biodiversity
allow predictions about the potential spread of exotic mosquito introductions
allow predictions about the potential effects of global warming on mosquito distributions
allow insights into mosquito community structure and mosquito environmental and climatic correlates to species occurrence (ecological niche)
allow continent-wide rather than just local studies of vector-borne disease
Identifying cryptic evolutionary lineages that differ in geographic or ecological space.



The Mal-area calculator

A novel enhancement of VectorMap is the Mal-area calculator (MAC) that quantifies the overlap between vector and pathogen distribution models, and host (human) population. The co-occurrence of vectors, parasites and hosts are required for many vector-borne diseases, and the MAC quantifies this co-occurrence for a given area, thus potentially providing a map and simple index of disease risk for any area of interest. At the moment the MAC is at the 'proof of concept' stage, but we plan to roll out an operational version in the near future!



VectorSurv

An associated application in preparation is VectorSurv, designed to host longitudinal survey data for arthropod vectors. Data from trap sites that are routinely monitored, often over many years, provides a valuable resource for assessing disease transmission risk, and for identifying the climatic and phenological factors responsible for temporal changes in abundance. VectorSurv is designed for online input and display of surveillance data.

For best performance, set screen resolution for 1024 x 768 or greater, and use IE 6.0 or greater, FireFox 2.5 or greater, or Safari 3 or greater.

The quality and completeness of data cannot be guaranteed. Users employ these data at their own risk. By downloading and/or viewing data on the MosquitoMap, SandflyMap, and TickMap portals, you are agreeing to these conditions.

OPEN MosquitoMap

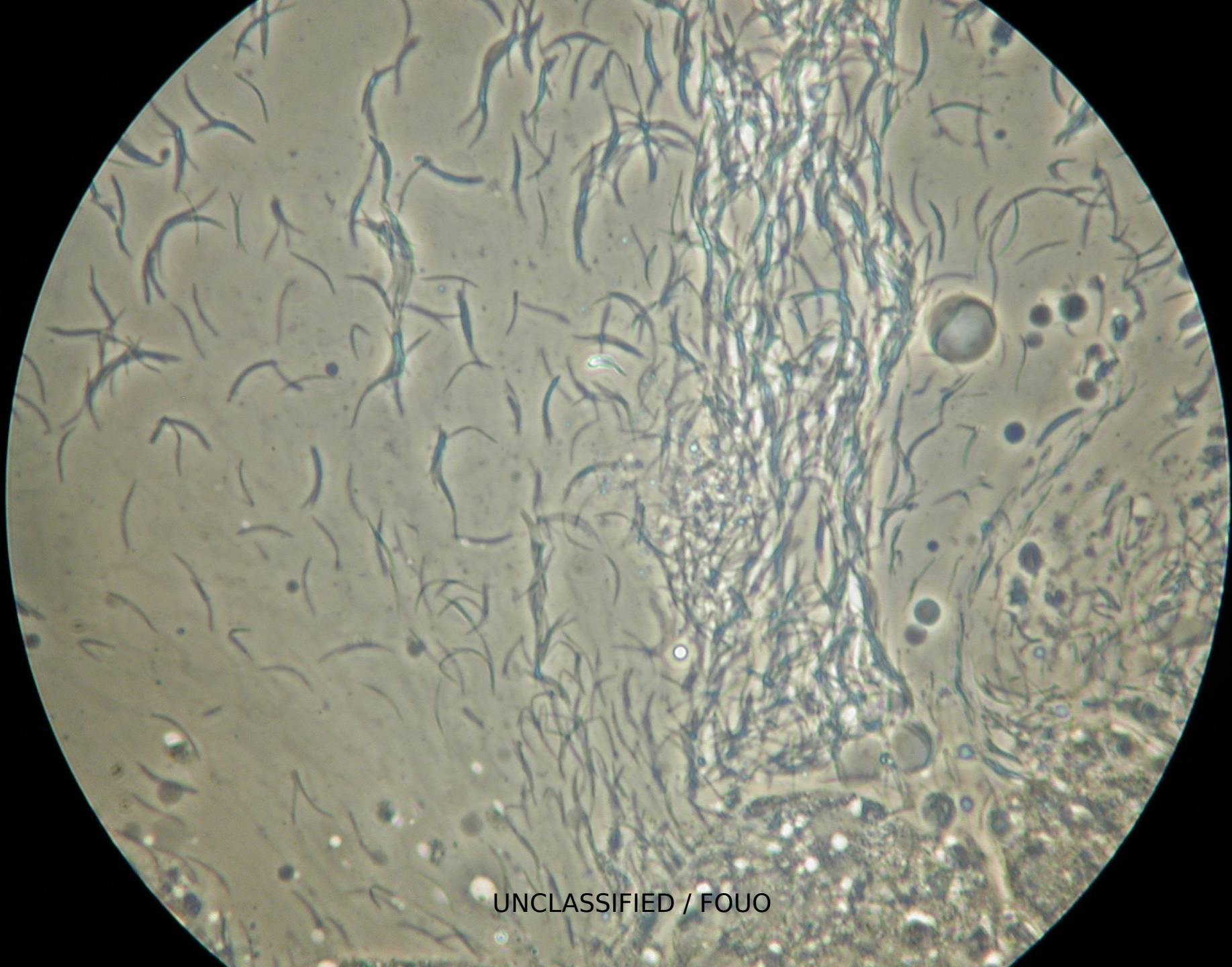
OPEN TickMap

OPEN SandflyMap





UNCLASSIFIED / FOUO



UNCLASSIFIED / FOUO

Malaria Parasites and Their Life Cycles

- Four human forms of malaria
 - *Plasmodium vivax*
 - 48h cycle, young RBCs, worldwide
 - *Plasmodium malariae*
 - 72h cycle, older RBCs, worldwide
 - *Plasmodium ovale*
 - 48h cycle, young RBCs, Africa
 - *Plasmodium falciparum*
 - 48h cycle, all RBCs, Tropical regions

Prepatent & Incubation Periods (parasites in blood vs. illness)

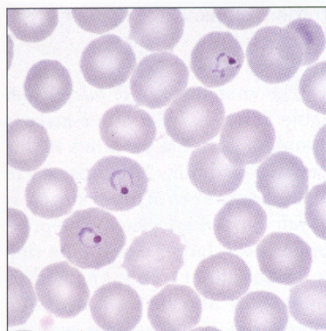
SPECIES	PREPATENT PERIOD	INCUBATION PERIOD
<i>P. falciparum</i>	11 - 14 days	8 - 15 days
<i>P. vivax</i>	11 - 15 days	12 - 20 days
<i>P. ovale</i>	14 - 26 days	11 - 16 days
<i>P. malariae</i>	21 - 28 days	18 - 40 days

Plasmodium knowlesi

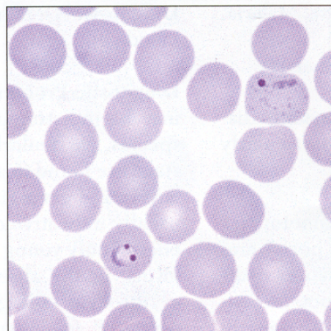
- Simian species of malaria naturally infecting macaques in Southeast Asia
- Resembles human species by microscopy
 - *P. malariae* (affects any age cell like *P. falciparum*)
- 24 hour replication cycle
 - Can cause severe and fatal infections
- Large numbers of human cases reported initially from Malaysian Borneo
- Subsequent reports of human cases in Peninsular Malaysia, Singapore, and the Philippines

Diagnosis

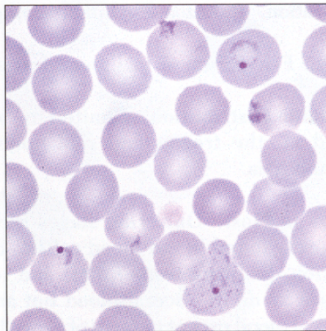
- Gold standard – Giemsa thick & thin smears
 - Species and parasite density determined
 - Labor intensive, modest cost
 - False negative circumstances
 - Parasites not present in circulation
 - False positive circumstances
 - Parasites seen may not be the cause of fever in endemic areas (Kisumu example of misdiagnosis...)
 - In highly endemic areas, clinical diagnoses made



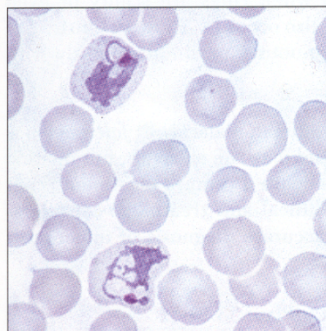
1



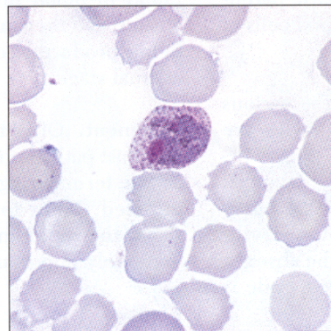
2



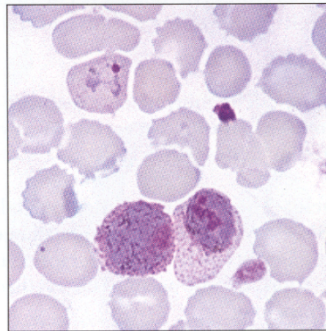
3



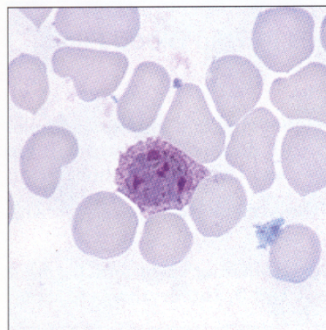
4



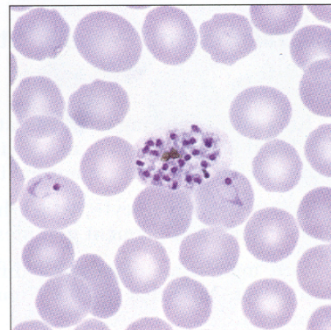
5



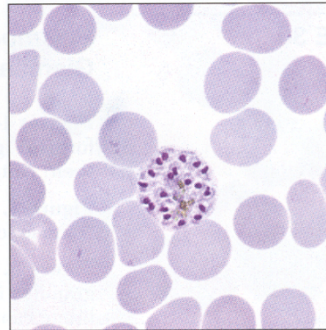
6



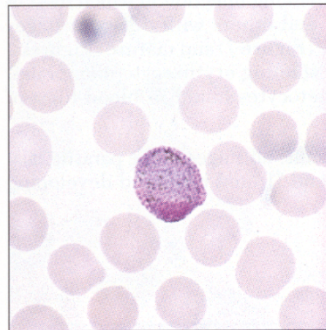
7



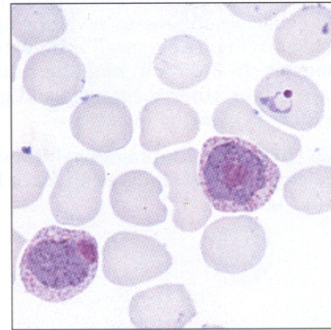
8



9



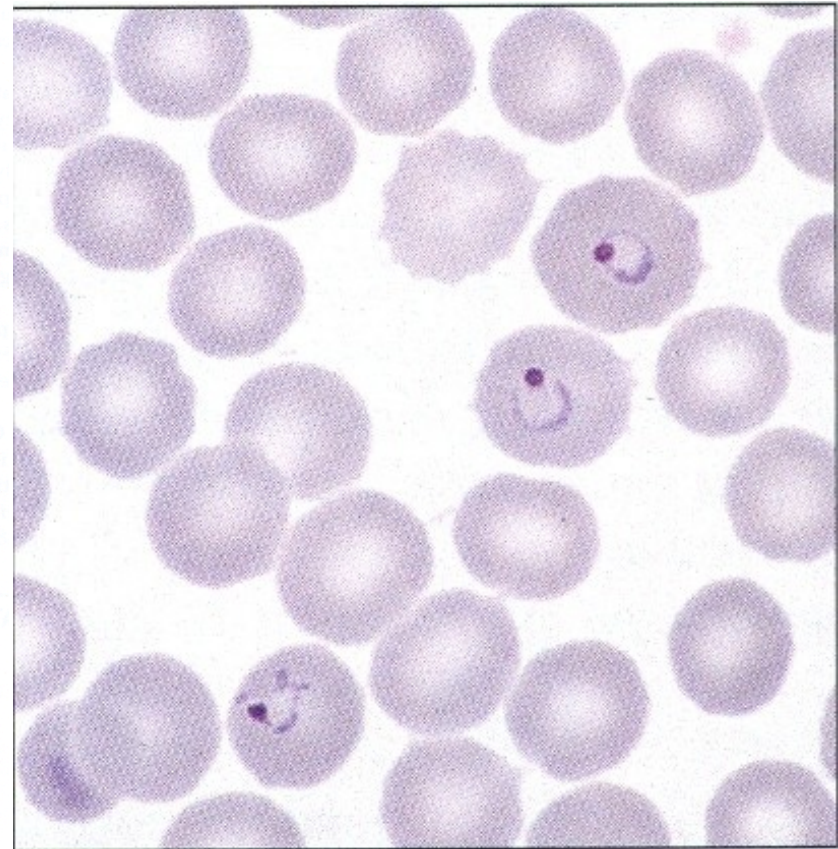
10



11

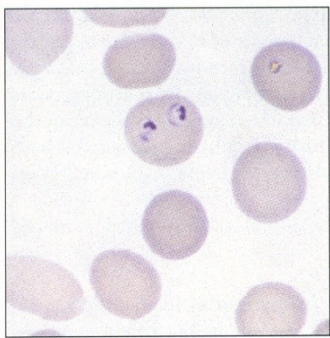


12

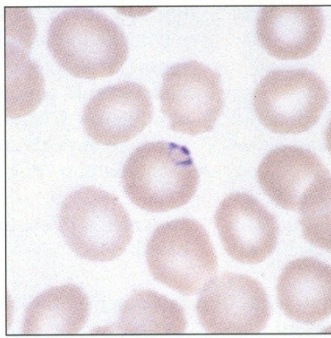


*Plasmodium
vivax*

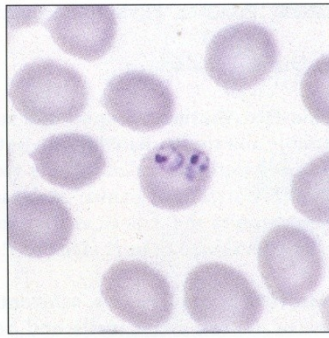
UNCLASSIFIED / FOUO



1



2



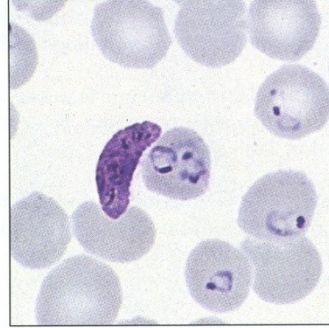
3



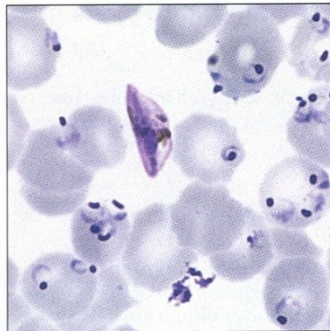
4



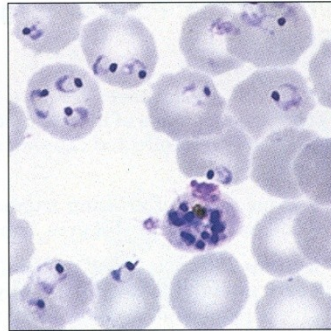
5



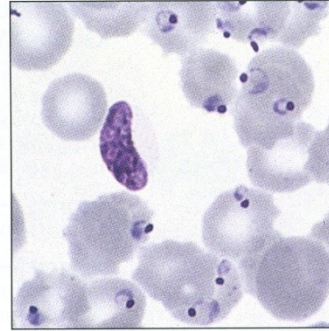
6



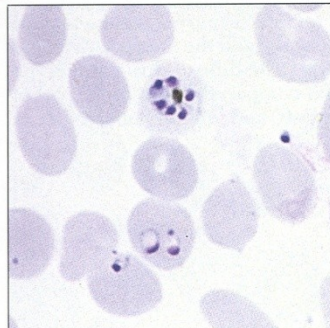
7



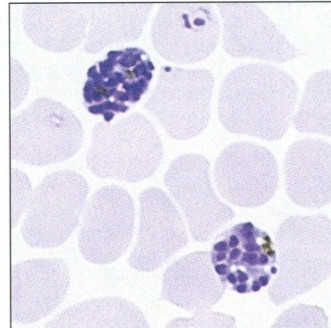
8



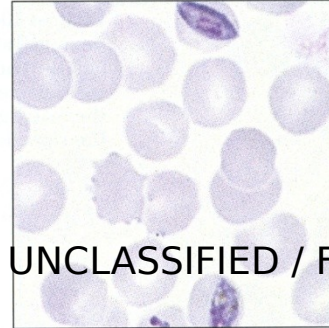
9



10



11



12



Plasmodium falciparum

UNCLASSIFIED / FOUO



UNCLASSIFIED / FOUO

Rapid Diagnostic Tests

- Currently acceptable test(s)
 - *Binax Now*, Inverness Medical Innovations, Inc.
- Reliability
 - False negatives – Prozone Effect
 - Hyperparasitemia – too much antigen
 - HRP-2 assays (16/17) most affected; pLDH and aldolase not affected
- Follow-up
 - FDA ‘clearance’ Labeling – what does it actually say?

NOW[®] ICT Malaria (Binax, Inc., Portland ME)



- Less than 15 minutes
- Non-microscopic
- Single reagent
- Minimally-trained operator
- Environmentally robust
- RDTs will NOT replace malaria microscopy
 - Confirmatory test for species, parasite density
 - Back-up to rule out inaccurate results

Parasite Growth in the Blood

Log+ increase in parasites per 48-hour cycle (for *P. falciparum*)

Threshold	Parasite mia	Parasites/ml	Parasite burden
Expert Microscopy	0.0005%	20-50/ml	10^8 parasites
Symptoms in non-immunes	0.002%	100/ml	10^9 parasites
Malaria RDT	0.005%	100-1000/ml	10^{9-10} parasites
Severe malaria	2%	100,000/ml	10^{12} parasites
Death	10%	500,000/ml	10^{13} parasites

- *“Good doctors are useless without good discipline. More than half the battle against disease is fought not by doctors, but by regimental officers. It is they who see that the daily dose of mepacrine is taken, that shorts are never worn, that shirts are put on and sleeves turned down before sunset. . . I therefore had surprise checks of whole units, every man being examined. If the overall result was less than 95% positive, I sacked the commanding officer. I only had to sack three; by then the rest had got my meaning.”*

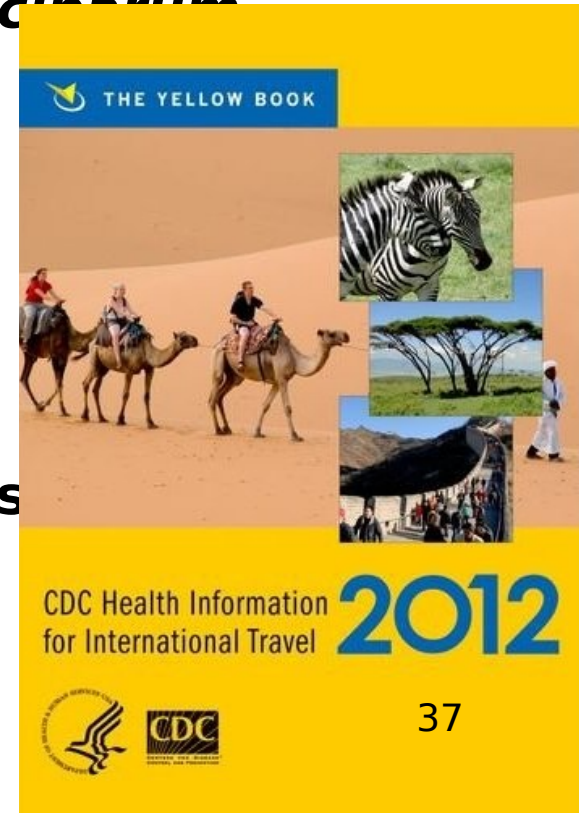
General Slim, Burma Campaign, WW II
(Under General Slim, the malaria rate in troops decreased from 12 per 1,000/day to 1 per 1,000/day)

UNCLASSIFIED / FOUO



Malaria Treatment US '2012'

- **Intravenous treatment of severe malaria**
 - Quinidine gluconate
 - Treatment IND with IV Artesunate
- **Oral treatment of uncomplicated *P. falciparum* malaria**
 - Proguanil / atovaquone (Malarone®)
 - Artemether-lumefantrine (Coartem®)
 - Quinine sulfate + doxy or PS
 - Mefloquine (Lariam®)
 - Chloroquine (Aralen®)
- **Available and can be used (Rx adjuncts)**
 - Doxycycline, clindamycin, azithromycin
- **Radical cure of relapsing malaria**
 - Chloroquine + primaquine





UNCLASSIFIED / FOUO

CDC's Compassionate Use IND

- WRAIR produced 1,000 vials of the “clinical lot” for compassionate use (another 10,000 vials being produced now – available in May 2010)
- CDC has a Compassionate Use IND for IV AS
 - Compassionate Use IND went into effect on 21 June, 2007
 - Complete cross-reference to U.S. Army IND for IV AS
 - Administered by Domestic Response Unit & Malaria Branch
 - Announcement Made on 03 August, 2007 in MMWR
- Now released to Canadians, and will

UNCLASSIFIED / FOUO

Evidence of Artemisinin-Resistant Malaria in Western Cambodia

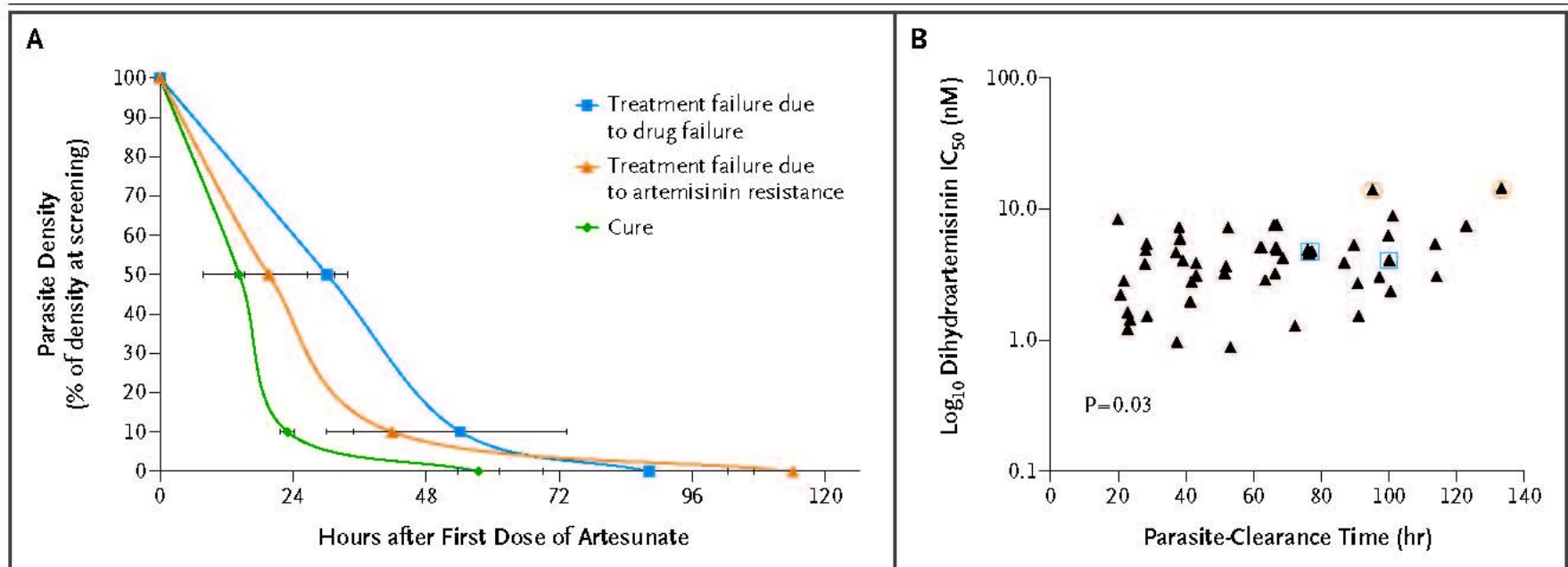


Figure 1. Parasite Density, Parasite-Clearance Time, and 50% Inhibitory Concentration (IC_{50}) among Patients Receiving Artesunate, According to Clinical Outcome.

Panel A shows the parasite-reduction curves for the 56 patients who were cured, the 2 patients classified as having artemisinin-resistant infections, and the 2 with drug failures (i.e., patients who had recrudescence but who were not classified as having artemisinin-resistant infection, since the drug level was inadequate). The data points and horizontal I bars denote the means and standard errors. Panel B shows the parasite-clearance times in the artesunate group, as compared with the IC_{50} for dihydroartemisinin ($R=0.31$, $P=0.03$). Orange circles indicate patients whose infection was classified as artemisinin-resistant, and blue squares patients in whom treatment failed but whose infection was not classified as resistant.

UNCLASSIFIED / FOUO

40

DRUG

PROBLEMS

Artemisinin	Recrudescence, Neurotoxicity
Atovaquone	Resistance
Azithromycin	Limited efficacy
Chloroquine	Resistance
Doxycycline	Phototoxicity, GI intolerance
Fansidar	Resistance, Allergic Rxns
Halofantrine	Cardiotoxicity
Mefloquine	Resistance, Psychiatric effects
Primaquine	Narrow Therapeutic Index
Proguanil	Resistance, Mouth ulcers
Quinidine gluconate	Going off the market?
Quinine	Resistance, Tinnitus

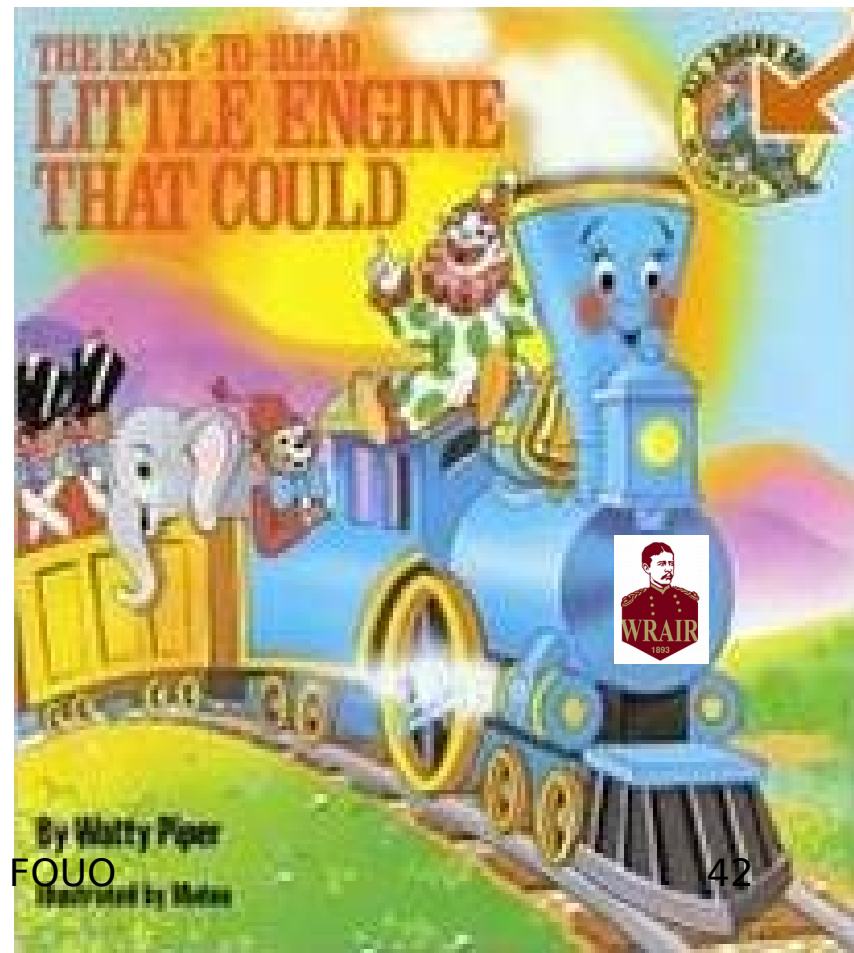
DoD Antimalarial Drug Program

The Biggest Little Drug Company in the World

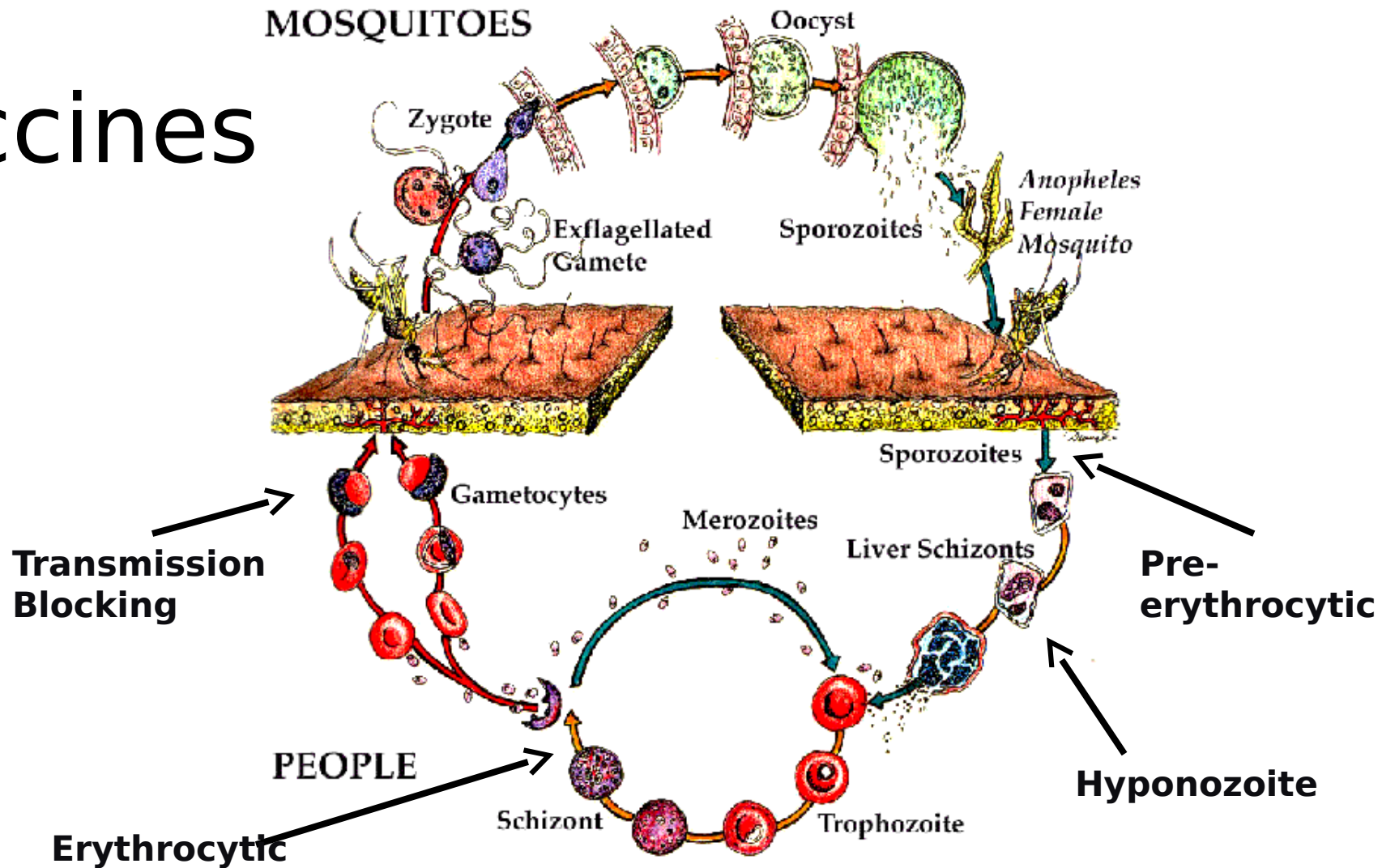
- Filed 63 IND's with US FDA

- Chloroquine
- Primaquine
- C-P Tablets
- Mefloquine
- Doxycycline
- Halofantrine
- Fansidar
- Malarone

UNCLASSIFIED / FOUO



Vaccines



Approaches to Control

- Vector Control Methods
 - Breeding site control, larvacide, adulticide, bed nets and personal protection
- Treatment Strategies
 - Passive case finding and self-referral
 - Home treatment early in course of disease
 - Prophylaxis in selected groups

Controversies in Malaria

- **Prophylaxis... drug to use?**
 - Mefloquine vs. Malarone vs. Doxycycline
- **Prophylaxis... to do or not?**
 - Short-term vs. Long-term Deployments
- **Prophylaxis... duration?**
 - Continuous vs. Interrupted
- **RDTs...**

Malaria

Take Home Points

- Malaria continues to evolve, not just in resistance, but in new species
- Malaria is as important a consideration for force health protection today as ever
- Malaria is not just a force health protection issue, but a strategic stability operations consideration in the global war on terrorism
- We have more tools today than ever, but we can lose them at any time and we must understand and respect their limitations

Reality – Case study

- 45 y/o Male from Ivory Coast. Lived there 20 yrs ago and now owns property and visits every few years
- Last visit 2008 and took prophylaxis. Went this year from Feb to mid-Mar and had an uneventful stay but did not take prophylaxis
- Returned 15Mar and on the 24th or so got fevers/chills and rigors
- Used OTCs 1 day, had syncope while at work
- Civ ER via EMS on the 26th. Labs sig only for platelets 60s and dx falciparum malaria by giemsa with 0.7% parasitemia
- Give him a script of oral quinine and doxy. He took doxy but was unable to fill oral quinine due to pharmacy availability (cost)
- On the 28th felt worse. Parasitemia now 0.5% and labs the same with platelet 46 main abnormality other than mild prerenal azotemia
- Response to malarone po first 24hr in ICU and d/c after 3rd day
- 14d of primaquine given due to overabundance of caution. Seen Monday and he was doing well



UNCLASSIFIED / FOUO

Fighting Malaria

- **Requires expensive, sustained efforts**
- **Medical facilities are not equipped to quickly and accurately diagnose and effectively treat malaria**
- **Effective control efforts if subsidized and applied**
 - **Indoor Residual Spraying (IRS) with DDT - saves lives**
 - **Insecticide Treated Bed Nets (ITNs) - save lives**
 - **Artemisinin combinations treatment - saves lives**
 - **Improved diagnosis - use expensive drugs for those that need it**
 - **World is waiting for a malaria vaccine**
- **Eradication requires multiples efforts and multiple solutions**



“Science is not an accessory occupation for man but an essential activity...”

Teilhard de Chardin

“The Phenomenon of Man”

UNCLASSIFIED / FOUO

QUESTIONS?

COL Arthur Lyons

Arthur.g.lyons.mil@health.mil

Commercial: 703-692-8918